1131-135 Sildenafil Selectively Improves Endothelium-Dependent Microcirculation

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Background: Sildenafil, a selective phosphodiesterase-type-5 (PDE-5) inhibitor, may cause systemic vasodilation and consequent mild decreases in blood pressure. Nitric oxide mediated vasodilation to skin and skeletal muscle in the forearm would be enhanced if PDE-5 were present in resistance vessels. The effect of PDE-5 inhibition on endothelium dependent and independent vasodilation is not known. We tested the hypothesis that sildenafil would enhance forearm blood flow to skin and skeletal muscle at rest in a thermoneutral setting.
Methods: We studied 10 middle-aged healthy male volunteers (age 43±2 years) who were randomized in a double-blind, crossover fashion to receive a single oral dose of sildenafil 100 mg or placebo on 2 separate study days. At each study visit, bilateral forearm vascular resistance (FVR) and skin vascular resistance (SVR) responses were evaluated during intrabrachial infusion of acetylcholine (3, 10 and 30 mcg/min), an endothelium-dependent vasodilator, sodium nitroprusside (1, 3 and 10 mcg/min), an endothelium-independent vasodilator, and verapamil (30, 100 and 300 mcg/min). Plasma norepinephrine was measured at baseline and at 60 minutes following study drug administration.
Results: FVR responses to acetylcholine, sodium nitroprusside, and verapamil decreased following sildenafil administration and were each similar to placebo (p=NS). The change in SVR from baseline after sildenafil at each dose of acetylcholine decreased by -7±9%, -22±12%, and -37±11% (p=0.006): SVR responses with placebo were 14±8%, 9±9%, and −1±11% (p=NS). Compared to placebo, SVR responses to acetylcholine were significantly decreased after sildenafil (p=0.02). Plasma norepinephrine increased by 58±19% following sildenafil and 20±19% following placebo (p=0.003).
Conclusion: Sildenafil selectively improved blood flow to skin in healthy middle-aged men suggesting that PDE-5 may play a role in resistance vessel function. Increases in blood flow to skeletal muscle, which is influenced to a greater extent by tonic sympathetic tone, may be masked by sildenafil induced sympathetic activation.

1131-136 Dietary Green Tea Intake Preserves and Improves Arterial Compliance and Endothelial Function

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Introduction and hypothesis: Although Japanese are highly exposed to smoking habits, hypertension, diabetes mellitus, and recently increasing serum cholesterol levels, incidence of cardiovascular events remains lower in Japan. We assessed hypothesis that green tea, a representative dietary antioxidant in Japan, influences vascular function.
Methods: We evaluated taste for green tea, and we noninvasively quantified brachial-to-ankle pulse wave velocity (PWV), and we also quantified flow mediated dilation of right brachial artery after transient forearm occlusion for 5 minutes (FMD) and after sublingual administration of glyceril trinitrate (TNG) using high resolution ultrasonography in 150 ambulatory Japanese aged 60 or older. Taste for green tea was graded by daily green tea intake. Group-G included the subjects drinking no less than 800ml or 5 cups of green tea; and group-C included the rest subjects. We compared serum variables, PWV, FMD, and TNG between the 2 groups. We evaluated changes those variables 4 months after those in group-C increased green tea intake.
Results: Between the 2 groups there was no significant difference in TNG. Some of lipid and glycemic levels were lower in group-G (n=77) than group-C (serum total cholesterol; 192±28mg/dl versus 182±24mg/dl, p=0.03). PWV was significantly smaller in group-G than in group-C (1542±256cm/s versus 1765±225cm/s, p< 0.01). FMD was significantly larger in group-G than in group-C (8.3±5.0% versus 5.6±4.1%, p<0.01). PWV (from 1742±268cm/s to 1621±286cm/s, p<0.01) and FMD (from 5.7±4.3% to 7.5±4.9%, p<0.01) were significantly improved after they increased green tea intake. **Conclusion:** In conclusion dietary intake of green tea pleitropically protects Japanese from atherothrombogenic process reducing several risk factors, preserving arterial compliance and endothelial function, and may contribute to low incidence of cardiovascular events in Japan.

1131-137 Effect of Caffeine on Arterial Stiffness and Endothelial Function

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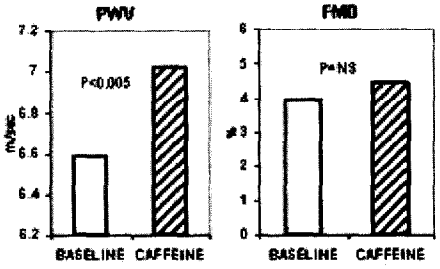
Background: Caffeine (C) is the most widely used pharmacological substance. However, its effects on arterial function have not been adequately investigated. Arterial function is an important determinant of cardiac performance and a prognosticator of cardiovascular risk. We investigated the effect of C on arterial stiffness and on endothelial function.
Methods: The effect of 250 mg of C (equivalent to 2-3 cups of coffee) was studied in 27 healthy subjects (age 34±11 yrs) in a randomized, placebo-controlled, crossover protocol. Arterial stiffness was evaluated by carotid-femoral pulse wave velocity (PWV, n=10) over 3 hours using a validated, automated, non-invasive device (Complior®). Endothelial function was evaluated at peak effect (30 min) by measuring brachial artery flow-mediated dilatation (FMD-high frequency ultrasound) after reactive hyperemia induced by cuff occlusion (n=17).
Results: Systolic and diastolic pressure increased significantly (by 8.7 and 7.1 mmHg respectively; P<0.001 for both) with C. PWV increased significantly (by 0.43 m/sec) denoting an increase in aortic stiffness (figure). However, FMD did not change (figure) denoting no change in conduit artery endothelial function. Likewise, nitroglycerin-mediated dilatation did not change.



Conclusions: Caffeine increases stiffness of large arteries, a finding that has important implications for left ventricular function and coronary flow. This effect, however, is not mediated through changes in endothelial function.

1131-138 Enhanced Mobilization of Circulating Endothelial Progenitor Cells in Hypercholesterolemic Patients by 3-Hydroxy-3-Methylglutaryl Co-A Reductase Inhibitor: View Point to Two Different Types of Endothelial Progenitor Cells

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Background: Endothelial progenitor cells (EPC) are mobilized endogenously in respond to ischemia or exogenously by cytokine stimulation. In vitro study, 3-Hydroxy 3-Methylglutaryl Co-A reductase (HMG Co-A reductase) inhibitor enhances angiogenesis and function of EPC. To verify the mobilizing effect of HMG Co-A reductase inhibitor to EPC in human, we evaluate the number & function of EPC from peripheral mononuclear cells in hypercholesterolemic patients before & after statin treatment.
Methods: 22 pure hypercholesterolemic patients (Low density lipoprotein (LDL) cholesterol > 160mg/dl) were included. 10 normocholesterolemic young volunteers were evaluated simultaneously. Peripheral blood mononuclear cells were isolated at pre- & post-statin treatment (simvastatin 20mg/day, 4 weeks), and cultured with EGM-2 MV. Attaching cells (AT cells) were identified as EPC by UEA-1 staining and DiI- acetylated LDL uptake. Serial number and morphological changes of AT cells were observed at 4-5 random high-power fields (× 200).
Results: 1) In post-statin treatment, LDL cholesterol level was significantly lower (190 ± 31 vs 117 ± 51 mg/dl, P<0.001) and AT cells were increased in number (at 10^{th} culture day (D10): 3.3 ± 4.0 vs 7.8 ± 12.7 / high power field). The change of LDL cholesterol levels after statin treatment showed no correlation with number of AT cells. 2) 2 different types of EPC were observed in both hypercholesterolemic & normocholesterolemic groups. Spindle shaped EPC was observed in early period (D3-D10), showed lower proliferative activity and disappeared slowly at D10-21. HUVEC-like EPC was observed in later period (D14-D30) and showed high proliferative activity. 3) HUVEC-like EPC was observed more and earlier in post-statin than pre-statin in hypercholesterolemic patients (8/20 vs 4/20 paitents, D15±3 vs D38±21) and observed more in normocholesterolemia than hypercholesterolemia (3/10 vs 4/20 paitents).
Conclusion ; Hypercholesterolemic patients have less number of EPC than young normocholesterolemic persons. After Simvastatin treatment, the number of 2 types of EPC were significantly increased. This finding suggests the possible role of simvastatin mobilizing EPC in humans

1131-139 Prognostic Value of Epicardial Coronary Artery Dysfunction in Type 2 Diabetic Patients With Angiographically Normal Coronary Arteries and Without Other Coronary Risk Factors

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Background: coronary artery disease is a leading cause of death in diabetic patients (DP). Epicardial coronary endothelial dysfunction predicts cardiovascular events in patients with coronary risk factors. This study was designed to evaluate outcome of type 2 diabetic patients with angiographically normal coronary arteries on the basis of their epicardial coronary endothelial function. Methods: 128 patients (53 control subjects [CS], 42 males, 11 females [51.7±6.4 years]) and 72 DP, 38 males, 34 females [50.3±8.5 years]) with normal coronary arteries and without any other coronary risk factor underwent epicardial coronary reactivity assessment to cold pressor test (CPT) using quantitative coronary angiography. Unpredictable cardiovascular events (CVE) (sudden cardiac death, stable and unstable angina, myocardial infarction, stroke, angioplasty, coronary artery surgery) were recorded with a mean follow-up of 45 months (range 27-68). Results: in CS, mean diameter change was +16.3±8.6%, there was no constriction, dilation occurred in 90.6% of the subjects, and no change in 9.4%. In DP the response was strikingly different: mean diameter decreased by 14.4±12.1%, there was no dilation, constriction occurred in 73.6%, and no change in 26.4%. Endothelium-independent dilation to nitrates was normal in the 2 groups (26.8±13.5% and 24.9±14.3%, respectively, NS). During follow-up, there was only one CVE (transient ischemic attack) in CS. In DP, there was 26 CVE in 18 patients (25%, p<0.01 vs CS). In these patients, there was 22 CVE in 16/53 patients (30,2%) with coronary artery constriction, and 3 CVE in 2/19 patients (6.3%) with no change in coronary artery diameter (p<0.05). Conclusion: epicardial coro-